REMARKS:

Specification Amendments:

As the examiner can see, page 5, lines 23-25 have been amended to state that the two nucleotide sequences correspond to 1917-1937 of SEQ ID NO. 1, sense and anti-sense. Support for this amendment may be found for example in Figures 16 and 17 and the filed sequence listing.

Page 9, line 25 has been corrected to state that the sequence shown in Figure 17 corresponds to SEQ ID No. 12, not SEQ ID No. 2. Support for this amendment may be found in Figure 17 and the filed sequence listing.

Page 10, line 10 has been corrected to state that the amino acid sequence of CRT shown in Figure 13 corresponds to SEQ ID No. 23, not SEQ ID No. 3. Support for this amendment may be found in Figure 16 and in the filed sequence listing.

In addition, page 16 has been corrected to state that the SM22 α promoter utilized was 1343 base pairs, not 445 base pairs. It is noted that support for this amendment may be found at least in Figures 16 and 17 and SEQ ID Nos 1 and 12.

Claim Amendments:

As amended, claim 1 is directed to a transgenic mouse whose genome comprises SM22α promoter operably linked to a cDNA encoding a calreticulin (CRT) peptide having at least 60% homology to SEQ ID No. 23. Expression of calreticulin from the SM22α promoter in the vascular smooth muscle cells of the transgenic mouse results in hemangioma formation. Support for these amendments may be found in claim 2, now cancelled, and on page 10, lines 4-14 and page 11, lines 9-13.

New claims 12-14 which depend on claim 1 have been added. Support for these claims may be found on page 10, lines 4-14, Figure 16 and the sequence listing as filed.

As amended, claim 3 is directed to a transgene comprising SM22α promoter operably linked to a cDNA encoding a calreticulin peptide having at least 60% homology to SEQ ID No. 23. Support for this amendment may be found on page 10, lines 4-14.

New claims 18 and 19 which depend on claim 3 have been added. Support for these claims may be found at least on page 9, line 23, page 11, lines 9-19, Figure 16 and the sequence listing as filed and at least on page 9, line 25, page 11, lines 20-26, Figure 17 and the sequence listing as filed, respectively.

Claim 4 has been amended to be directed to a method for producing a transgenic mouse having symptoms similar to hemangioendothelioma comprising introducing into a fertilized mouse egg a transgene comprising SM22α promoter operably linked to a cDNA encoding CRT a calreticulin (CRT) peptide having at least 60% homology to SEQ ID No. 23; transplanting the injected egg in a foster parent female mouse; and selecting a mouse derived from an injected egg whose genome comprises SM22α promoter operably linked to a cDNA encoding a calreticulin peptide, said peptide having at least 60% homology to SEQ ID No. 23. Support for these amendments may be found at least on page 10, lines 4-14 and page 10 line 28 to page 11, line 4. Regarding the phrase "symptoms similar to hemangioendothelioma", it is believed that this would be understood by one of skill in the art, particularly in view of page

10, lines 15-19, page 12, lines 5-16, page 13 line 28 to page 14, line 22 and page 16, line 29 to page 19, line 17.

New claims 15-17 which depend on claim 4 have been added. Support for these claims may be found on page 10, lines 4-14, Figure 16 and the sequence listing as filed.

Claim Rejections

Claims 1-5 were rejected under 35 USC 112 for being directed to non-enabled subject matter.

As the examiner can see:

Claim 3 has been amended so as to directed to a transgene comprising a nucleic acid sequence encoding calreticulin operably linked to a SM22α promoter.

Claim 1 has been amended so as to be directed to a transgenic mouse comprising a nucleic acid sequence encoding calreticulin operably linked to SM22α promoter, wherein the transgenic mouse exhibits hemangioma formation.

Claim 4 has been amended so as to be directed to a method of making a transgenic mouse comprising a nucleic acid sequence encoding mouse calreticulin operably linked to SM22α promoter wherein the transgenic mouse exhibits symptoms similar to Kasbach-Merritt syndrome.

Regarding undue experimentation in regard the selection of any promoter, as discussed above, the claims have been limited to a SM22α promoter.

Regarding the need to teach the skilled artisan the parameters of what was used as a promoter, it is noted that claims 1 and 4 state that expression of calreticulin from the SM22α promoter in vascular smooth muscle cells is sufficient to result in hemangioma formation. Thus, the parameters of the SM22α promoter are defined in the claim – expression must occur in the vascular smooth muscle cells and expression must be of a sufficient level to result in hemangioma formation.

It is further noted that suitable SM22α promoter elements which target gene expression to vascular smooth muscle cells are well-known in the art and as such selecting other suitable SM22α promoter elements is clearly within the ability of one of skill in the art and would not require undue experimentation. The examiner is directed to the following references (copies provided): Akyurek et al., 2000, Mol Med 6: 983-991; Hoggatt et al., 2002, Circ Res 91: 1151-1159; Kim et al., 1997, Mol Cell Biol 17: 2266-2278; and Moessler et al., 1996, Development 122: 2415-2425; which describe the use of different SM22α promoter fragments. It is held that one of skill in the art could select suitable promoter elements by consulting the prior art and easily select promoter fragments known to have similar activity to the promoter element used in the instant application without experimentation. It is further noted that expression of proteins by the SM22α promoter is well-known in the art, as evidenced by at least Ribault et al., 2001, Circ Res 88: 468-475; and Ruchoux et al., 2003, Am J Pathol 162: 329-342. However, it was not known that expression of CRT in vascular smooth muscle cells would result in development of symptoms similar to hemangioendothelioma. It is therefore respectfully requested that the examiner reconsider this objection, as it is clear that suitable SM22α promoter elements are well known in the art.

Regarding the transgene comprising a nucleic acid encoding CRT obtained from any species of animal, it is noted that the claims have been amended to state that the calreticulin has 60% homology to the mouse calreticulin peptide.

Regarding the unreliability of maintenance of protein function between animals, it is noted that as discussed on page 14, line 23 to page 15, line 4, the calreticulins have a high degree of identity among species, as supported by the enclosed cDNA and amino acid comparisons. Homology of CRT from different species is also discussed in Michalak et al., 1999, Biochem J. 344: 281-292 (copy enclosed). In view of the high degree of identity amongst CRT, it is respectfully requested that the examiner reconsider this rejection as it is clearly a reasonable prediction that related peptides would have similar function.

Claims 1-5 were rejected under 35 USC 112 for containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is believed that the amendments to the claims and the arguments forwarded above overcome these objections.

Claims 1 and 4 were rejected under 35 USC 102(b) as anticipated by Nakamura. It is believed that the amendment of claims 1 and 4 to state that the promoter is SM22α and the arguments forwarded above in regard the USC 112 objections overcomes this objection. Specifically, Nakamura describes the cardiac overexpression of calreticulin using the α-MHC promoter. This promoter overexpresses the protein only in the cardiac myocytes and not in the vascular smooth muscle cells. As such, the phenotype hemangioma formation is not obtained by Nakamura and is not predicted by Nakamura.

Claims 1, 3 and 5 were rejected under 35 USC 103(a) as unpatentable over Dai et al in view of Li. Dai shows that injecting purified calreticulin protein in the blood stream before balloon angioplasty inhibits restenosis. It is respectfully noted that restenosis has nothing to do with development of hemangioendothelioma. Restenosis is developed due to proliferation of smooth muscle cells and migration of smooth muscle cells through the endothelium into the vascular lumen and closure of the vessel lumen (seen after angioplasty). However, hemangioendothelioma is a case of proliferation of the endothelial cells and development of a tumor which is phenotypically very different from restenosis. The novelty of the instant invention is that specific overexpression of calreticulin in vascular smooth muscle cells leads to the development of hemangioma (hemangioendothelioma). It is further noted that Dai used

exogenously added purified protein and did not introduce CRT cDNA into the smooth muscle cells, as was the case in the instant invention.

It is believed that the above arguments and the amendments to the claims overcome the objections.

Further and more favorable consideration is respectfully requested.

Respectfully submitted

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